

# The compound eye of flies divulges evolutionary secrets: analysis of fly eye development may shed light on human eye disease

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The *Pax6* group of genes belongs to a larger class of homeobox-containing genes, found in organisms from yeast to humans. They code for transcription factors and are distinguished by the presence of a specific DNA-binding motif (a homeodomain) that serves to regulate gene expression. The "helix-turn-helix" 3D structure of the homeodomain is the same structure that is seen in bacterial gene regulatory proteins, suggesting that this is an ancient conformation that has been conserved throughout billions of years of evolution.

In mice, sea squirts, and squid, *Pax6* has been shown to activate the program that leads to eye formation during the development of the organism. In mouse, where the *Pax6* gene is expressed in the developing eye and brain, a mutation called *Small eye (Sey)* results from defects in *Pax6*. This makes it a good model for studying aniridia, a condition caused by a mutation in human *Pax6* in which an incomplete iris can lead to poor vision, light sensitivity, and a tendency to develop progressive glaucoma.

Although the eyes of vertebrates have a single lens, the compound eye of *Drosophila* consists of about 750 units, each unit containing a lens, retina, and photoreceptor cells. Even so, parallels exist between these two types of eye. In flies, the eye

precursor cells differentiate into these distinct units at a distinct step of development, when *ey*, a *Pax6* homolog, can be detected.

Recently, a second *Drosophila Pax6* gene was reported and named *twin of eyeless (toy)*. Perhaps surprisingly, *toy* in some ways is more similar to the evolutionarily distant vertebrate *Pax6* proteins than to *Ey*. In particular, fly *Toy* and mouse *Pax6* have a similar DNA-binding pattern; they have a much higher affinity for DNA than *Ey*. This can be attributed to the mutation of a single residue (Asn? Gly) in a highly conserved part of *Ey*, known as the paired domain.

The existence of two *Pax6* genes in flies, but not in vertebrates, suggests that a gene duplication event occurred sometime during fly evolution. That *Toy* is more closely related to vertebrate *Pax6* suggests that *Toy* is the more ancient form, which gave rise to *Ey*. The key point in the evolution in these two genes was probably when the Asn?Gly mutation occurred, radically altering the DNA-binding function of *Ey*. At this point *Ey* could have become dependent on *Toy* for its activation, triggering a divergence in function of the two proteins. Today, genetic evidence suggests that *Toy* is found upstream of *Ey* in the regulatory pathway of eye development, and they each regulate distinct developmental events.



**The structure of the paired domain found in human *Pax6*** Two distinct domains are found in *Pax6* — a homeodomain and a paired domain. Recent interest has focused on the paired domain, mutations in which cause several human disorders, including aniridia. This figure depicts the structure as ribbons drawn through the main carbon backbone of the protein (red) and through the phosphate atoms of the DNA backbone (blue). Mutations in the paired domain interfere with the DNA-binding properties of *Pax6*, altering its function, and causing a detrimental effect on the health of an individual.

(Reproduced from Xu, H.E., Rould, M.A., Xu W., Epstein, J.A., Maas, R.L. and Pabo, C.O. (1999) 'Crystal structure of the human *Pax6* paired domain-DNA complex reveals specific roles for the linker region and carboxy-terminal subdomain in DNA binding' *Genes Dev.* 13, 1263-1275, with permission.)

### Box: Search PubMed for *Pax6* mutations

Click on the link below to start an html tutorial.

Find information on *Pax6* mutations [[http://www.ncbi.nlm.nih.gov/Coffeebreak/CB6\\_Pax/PQ1.html](http://www.ncbi.nlm.nih.gov/Coffeebreak/CB6_Pax/PQ1.html)]

### Box: Search GeneMap99 for *Pax6*

Click on the link below to start an html tutorial.

Where is *Pax6* found in the human genome? [[http://www.ncbi.nlm.nih.gov/Coffeebreak/CB6\\_Pax/GM1.html](http://www.ncbi.nlm.nih.gov/Coffeebreak/CB6_Pax/GM1.html)]

### Box: Use BLAST to search for proteins similar to *Pax6*

Click on the link below to start an html tutorial.

See how *Drosophila* Ey compares to other *Pax6* proteins [[http://www.ncbi.nlm.nih.gov/Coffeebreak/CB6\\_Pax/BQ.html](http://www.ncbi.nlm.nih.gov/Coffeebreak/CB6_Pax/BQ.html)]